REQUEST FOR ENTRY OF AMENDMENT TO DRAWING

Please replace Figures 1-6 as originally filed with the enclosed replacement Figures 1-6.

REMARKS

Claims 36, 38 and 45-47 have been amended. New claims 67-69 have been added. Claims 51-66 have been withdrawn from consideration as being directed to non-elected inventions. Thus, claims 36-69 are now pending in the present application, with claims 36-50 and 67-69 currently under consideration. Support for the amendment to claim 36 may be found in the specification at page 3, lines 20-21, and page 7, lines 14-15. Support for new claim 67 may be found in original claim 36. Support for new claim 68 may be found in original claim 11. Support for new claim 68 may be found in the specification at page 3, lines 23-33, and page 6, lines 16-18. Thus, no new matter has been added. Reconsideration and withdrawal of the present objection and rejections in view of the remarks presented herein are respectfully requested.

Request for Entry of Drawing Changes

As requested above, please replace Figures 1-6 as originally filed with the enclosed replacement Figures 1-6. The Examiner objected to the drawings under 37 C.F.R. § 1.83(a), stating that they were difficult to read. In the replacement figures, the characters and lines on the graphs are much more clear. No new matter has been added. Thus, entry of these drawing changes is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 36-50 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

The Office Action alleges that recitation of step (c) (the optional washing step) in claim 36 renders the claim indefinite, since it is not clear if this step is a part of the claimed invention. Although Applicants submit that claim 36 as filed clearly encompasses a process in which the washing step is included, as well as a process in which the washing step is not included, this claim as amended no longer recites the optional washing step. This step is now presented in new claim 67.

The Examiner also contends that claim 38 is indefinite, since it is allegedly unclear whether the term "anionic derivative of" extends to all species in the claim, or only to the species

immediately following the phrase. The Examiner's interpretation of the term "anionic derivative" as only extending to carboxymethyl cellulose is correct. Claim 38 as amended recites a Markush group in which "an anionic derivative of carboxymethyl cellulose is the last member, thus clearly indicating that the term "anionic derivative of" only applies to carboxymethyl cellulose.

In view of the comments presented above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. § 102(b)

Claims 36-41, 46 and 47 were rejected under 35 U.S.C. § 102(b) as being anticipated by Zhao (WO 00/46253). The Examiner alleges that Zhao discloses (Example 6 and claim 1) a method for producing a cross-linked gel wherein an alkaline solution of hyaluronic acid (HA) in sodium hydroxide is mixed with varied volumes of the epoxide 1,2,7,8-diepoxyoctane, drying the mixture into a gel formation, purifying (i.e., washing) the dried gel using acetone/water, acetone/isopropyl alcohol, and neutralising the gel in an acidic medium of acetone/hydrochloric acid at pH 5.

In order for a reference to anticipate a claim, all elements of the claim must be found within the reference. Zhao does not disclose all of the process steps recited in the present claims. In particular, Example 6 of Zhao discloses that HA and epoxide are mixed, then left for 24 hours during which time cross-linking occurs (page 24, lines 1-2). Thus, the cross-linking takes place *before* drying the gel over an additional 48 hour period. In contrast, the present claims recite that cross-linking occurs while the gel is being dried (see present Claim 36, step (b)). This drying step concentrates the reactants, thereby increasing the pH and creating unique cross-linking conditions, resulting in a cross-linked polysaccharide gel that is substantially resistant to hyaluronidase degradation. Thus, claims 36-41, 46 and 49 cannot be anticipated by this reference.

In addition, the presently claimed process results in a polysaccharide gel having a *single* type of cross-linkage. In contrast, Zhao discloses a process for forming *multiple* cross-linkages of HA or its derivatives with *two or more different types of cross-linking bonds*. This is evident from claim 1 of Zhao, which recites "[a] process for the preparation of *multiple* cross-linked

derivatives of hyaluronic acid, which process comprises cross-linking HA via *two or more* different functional groups". (Emphasis added). Similarly, the process described in Example 6 of Zhao results in a 'double cross-linked' HA gel (see page 24, lines 10-12).

In view of the comments presented above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103(a)

Claims 36-50 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zhao (WO 00/46253) in view of Mälson (WO 87/07898). The Examiner alleges that one of ordinary skill in the art would have a reasonable expectation of success in modifying the gel-producing method taught by Zhao with the freeze-drying gel preparation step taught by Mälson, since the combined teachings allegedly disclose the presently claimed method for producing a biologically active cross-linked gel composition. However, as discussed below, this combination of references does not render the presently claimed invention obvious.

The Examiner implies that the only differences between the instant invention and the process disclosed in Zhao are in relation to reaction parameters (e.g., pH, concentration, temperature). However, as discussed above, there are fundamental differences between the process of Zhao, which are not rectified by the teaching of Mälson, and which have a marked effect on the cross-linked polysaccharide products of the respective processes.

As discussed above, Zhao discloses cross-linked polysaccharides having multiple types of cross-linkages (see page 4, lines 22-25 and claim 1 of Zhao). The "advantages" said to be conferred by the process disclosed by Zhao relate only to hyaluronic acid (HA) having multiple types of cross-linkages (page 4, lines 19-20).

The process of Mälson also differs fundamentally from the presently claimed process in that Mälson describes a cross-linking process in which excess cross-linker is removed prior to drying (see page 3, second paragraph, and claim 1 of Mälson). In contrast, step (b) of present claim 36 recites that drying takes place without substantially removing epoxide. In the process recited in present claim 36, excess cross-linker is present during the drying step, during which the reactants become more concentrated and a high concentration of cross-linker and HA leads to a more cross-linked material than would result from the process disclosed by Mälson. Thus, by

teaching removal of excess cross-linking agent, Mälson teaches away from the presently claimed invention. Therefore, removal of excess cross-linker as taught by Mälson would result in a lesser degree of cross-linking in the resulting gel, which would result in a less desirable product, and would impair the operability of the presently claimed gel.

Moreover, a person skilled in the art would realize that the reaction parameters taught by Mälson would only apply to a process in which excess cross-linking agent (epoxide) has been removed prior to drying and subsequent treatment with acid. Thus, even if the reaction parameters taught by Mälson are combined with the disclosure of Zhao, one of ordinary skill in the art would not arrive at the presently claimed invention. Thus, the claims cannot be *prima facie* obvious in view of these references.

Unexpected results

The presently claimed process results in cross-linked polysaccharides having the surprising and advantageous property of being substantially resistant to hyaluronidase degradation (page 3, lines 23-33; page 4, lines 15-17; page 6, lines 16-18). Neither Zhao nor Mälson, either alone or in combination, teach or suggest a process (cross-linking during a drying step) that results in a cross-linked polysaccharide that is resistant to hyaluronidase degradation. In fact, Zhao and Mälson, respectively, teach away from the formation of a single type of cross-linkage and cross-linking occurring during the drying step. This unexpected property could not have been predicted based on these references, and would effectively rebut any allegations of *prima facie* obviousness if one were present.

In view of the comments presented above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or

other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

Applicants submit that all claims are in condition for allowance. However, if minor matters remain, the Examiner is invited to contact the undersigned at the telephone number provided below. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 11/26/08

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